Middle East Journal of Cancer; January 2020; 11(1): 1-11

Exposure to Non-Ionizing Radiation and Childhood Cancer: A Meta-Analysis

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Abstract

Background: A slight increase in the childhood cancer trend has been observed for the past few decades. Non-ionizing radiation is one of the environmental factors linked to childhood cancers. This review is conducted to assess the association between non-ionizing radiation and childhood cancer based on all original studies to date.

Methods: A systematic search was conducted on the titles and abstracts pertaining to non-ionizing radiation and childhood cancers using the PubMed, Scopus, SAGE and ScienceDirect databases from inception up to November 2018. Quality of each article was appraised using the Newcastle-Ottawa Scale, meta-analysis was performed with Review Manager, and fixed effects were used to estimate the pooled OR of the selected studies.

Results: A total of 15 articles met all the selection criteria. Twelve articles were included in the meta-analysis. Pooled risk estimates of the 12 studies, obtained via fixed effects model, showed that children exposed to 0.2 μ T or more of EMF non-ionizing radiation run 1.33 times higher risks of contracting childhood cancer compared to those with less than 0.2 μ T exposure (95% CI: 1.10, 1.60). The studies were statistically homogeneous (chi-squared *P*=0.71, I2=0%), and there was no evidence of publication bias.

Conclusion: It cannot be concluded that children exposed to non-ionizing radiation have higher risks of childhood cancer compared to those who were not exposed as claimed by the previous reviews. However, concerns about non-ionizing radiation exposure and childhood cancer should not be neglected.

Keywords: Non-ionizing radiation, Childhood cancer, Electromagnetic fields, Meta-analysis

Introduction

Childhood cancer is a rare disease that occurs before the age of 19.¹

These cancers account for less than 1% of the total cancer cases in highincome countries and 4% in low-income countries.² However, a

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slight increase in the childhood cancer trend has been noted for the past few decades. Several risk factors have been identified for childhood cancers,^{3,4} with many more yet to be explored. As widely known, ionizing radiation is one of the environmental factors linked to childhood cancers,^{5,6} while non-ionizing radiation is still classified as possibly carcinogenic to humans by the International Agency for Research on Cancer due to limited evidence of carcinogenicity in humans.⁷

Non-ionizing radiation refers to any type of electromagnetic radiation that does not carry enough energy to ionize atoms or molecules. However, it has sufficient energy for the excitation of an electron to a higher energy state, producing non-mutagenic effects in biological tissues.8 A few studies have been carried out over the past twenty years to assess whether non-ionizing radiation can pose potential health risks, especially cancer. Moreover, several systematic reviews and meta-analyses have been conducted to assess the association between non-ionizing radiation and childhood leukemia, where weak associations were observed due to the limited number of available case-control and cohort studies.⁹⁻¹² Therefore, this review aims to assess the association between non-ionizing radiation and childhood cancer based on all original studies conducted to date.

Methods

Search Methods

A systematic search was conducted on the titles and abstracts related to non-ionizing radiation and childhood cancer using PubMed, Scopus, SAGE, and ScienceDirect databases from inception up to November 2018. The keywords used in the search were "children, childhood, kids, adolescent, teenager, young, non-ionizing radiation, electromagnetic field, radiofrequency, microwave, tablet, phone, cordless, television, cancer, leukaemia, lymphoma, neuroblastoma and tumor". Articles were included if they were 1) original, 2) in English or Malay, and 3) based on the association between non-ionizing radiation

and childhood cancer. Four authors independently searched the articles in each database, and reviewed, assessed and decided on the selection of the articles to be included in the study.

Quality Assessment of Articles

Only articles that fulfilled the selection criteria were included in this study. The articles were then read and assessed independently by two reviewers. Quality of each article was appraised using the Newcastle-Ottawa Scale. The authors, institutions and journal of the articles were blinded to avoid bias during scoring. Final consensus was reached through discussion in case of discrepancy between the two reviewers during assessment. Data were extracted onto a standardized table.

Data Analysis

Fixed effects were used to estimate the pooled OR of the selected studies. The OR for each individual study was recalculated in order to obtain the crude OR and prevent non-standardized adjustment of risk estimates between studies. Heterogeneity was assessed by chi-squared test whereby a P-value<0.10 was considered as heterogeneous. Quantification of heterogeneity was then assessed by I2 statisticians; studies with a score of 25% to <50% were considered as mildly heterogeneous, 50% to <75% as moderately heterogeneous, and 75% or more as highly heterogeneous. However, the statistical test for heterogeneity was only to help the authors decide on the form of the necessary analysis, and the actual homogeneity of studies requires the assessment of the study design, population, sampling method, methods and tools for data collection, quantification of non-ionizing radiation and other characteristics. Publication bias was judged using a bias-assessment funnel plot. All analyses were performed with Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Relevant studies

The search was based on the titles and abstracts

from four databases, done independently by four authors who yielded 202 articles relevant to the topic (Figure 1). However, after combining the four databases, 160 duplicates were found and removed. Only 42 abstracts were screened, from which another 27 articles were removed because five were in other languages, twenty did not mention the association between non-ionizing radiation and childhood cancer, and the other two reported studies conducted in vitro. Full text articles were then read and assessed by the authors, and three more articles were excluded due to the cohort study design, where the association between non-ionizing radiation and childhood cancer was determined by questionnaire and different outcome units. A total of 12 articles were finally enrolled in meta-analysis.

Quality Assessment of Articles

A total of 14 articles that met all the selection criteria were assessed for the quality. Results

associated with the quality ratings of the retrieved studies are shown in table 1. Quality assessment was performed via Newcastle-Ottawa Scale (NOS), the most commonly used semi-quantitative quality assessment tool worldwide. Furthermore, it is a simple, convenient and validated instrument with a 'star system' to assess the quality of observational studies, which is to be included in a systematic review for a good interpretation of meta-analysis results.¹³ This quality assessment tool can be used for both case-control and cohort studies; in this study, NOS was employed with case-control studies subset. This instrument assesses a total of eight specific items under three quality dimensions: 1) selection of case and control groups (4 items), 2) comparability of case and control groups (1 item), and 3) ascertainment of exposure (3 items).¹⁴ Each item was given one star except for the comparability dimension which was given two stars. The NOS scale ranges between zero up to nine stars. A total score of 6



Figure 1. (Flow diagram of articles selection). From four databases search, there were 202 articles relevant to the topic, 160 duplicates were removed. 42 abstracts were screened and another 27 articles were excluded. Only 12 articles were finally enrolled in meta-analysis.

| Author (Year) | Case definition | Representative of cases | Selection of controls | Definition of controls | Comparability | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non- response rate | Total NOS score |
|---|--------------------|----------------------------|--------------------------|---------------------------|---------------|------------------------------|--|--------------------------|-----------------------|
| Tabrizi and Hosseini (2015) ⁽²⁶⁾ | * | | * | * | | | * | | 4 |
| Salvan et al. (2015) ⁽²²⁾ | * | * | * | * | ** | * | * | | 8 |
| Li et al. (2012) ⁽¹⁷⁾ | * | * | * | * | * | * | | | 6 |
| Malagoli et al. (2010) ⁽¹⁹⁾ | * | * | * | * | * | * | | | 6 |
| Kroll et al. (2010) ⁽¹⁸⁾ | * | * | * | * | * | * | * | | 7 |
| Kabuto et al. (2006) ⁽²³⁾ | * | * | * | * | * | * | * | | 7 |
| Schuz et al. (2001) ⁽²⁷⁾ | * | * | * | * | * | * | * | * | 8 |
| Day et al. (1999) ⁽²⁰⁾ | * | * | * | * | * | ** | * | | 8 |
| Green et al. (1999) ⁽²⁸⁾ | * | * | * | * | * | * | * | | 6 |
| Thomas et al. (1999) ⁽²⁹⁾ | * | * | * | * | * | * | * | | 7 |
| Dockerty et al. (1998) ⁽²⁴⁾ | * | * | * | * | ** | * | * | | 8 |
| Michaelis et al. (1998) ⁽²¹⁾ | * | * | * | * | ** | * | * | | 8 |
| Linet et al. (1997) ⁽³⁰⁾ | * | * | * | * | * | * | * | | 7 |
| Savitz et al. (1988) ⁽²⁵⁾ | * | * | * | * | * | * | * | | 7 |

and more indicated high-quality studies. One study was excluded due to a score of less than 6.¹⁵

Characteristics of Studies

15 studies assessed the association of nonionizing radiation and childhood cancer. Only three studies were conducted in Asia, while other studies were conducted in Europe, The United Kingdom, The United States of America, Canada, and New Zealand. The age of the study population ranged from one day to 15 years old. In determining the association between non-ionizing radiation and childhood cancer, various types of non-ionizing radiations were assessed in these 15 studies. The majority of the articles studied low frequency electromagnetic radiation (EMFs) produced by the high voltage power lines. There were two articles that evaluated the radiofrequency electromagnetic fields (RF-EMFs) from broadcast transmitters and mobile phone base stations.^{16,17} Therefore, these two articles had different outcome units, namely V/m and WYs/km² as shown in table 2.

In addition to different types of EMFs, there were also different levels of EMFs used to ascertain the association between EMFs and childhood cancer. Some studies reported categorized levels, while others reported mean or median EMFs values. Cut-off point of $0.2 \,\mu\text{T}$ was used as exposure level reference in the majority of studies.

Different EMFs exposure assessment methods were implemented in those 15 articles, each differing in terms of instrument selection, methods, locations and duration of measurements. The two common EMFs exposure assessments were personal monitoring or field measurements. Some studies did only instantaneous measurements, while some made 24-hour measurements and short-term or spot measurements. The majority of the studies made use of combined measurements to ensure the reliability of the obtained data (Table 2). The difference in exposure ascertainment was due to the type of wave-length, frequency or location of measurement and the respected protocol of assessment. Standard guidance or protocols for EMFs assessment was developed either by the national figures, responsible organizations in the field, or nonprofit agencies.

Besides, there were studies which used modelling to estimate the EMFs exposure to the population using the distance between the child's residence to the adjacent source of magnetic field¹⁸ or by geo-coding the high-risk or exposed residential areas.¹⁹ One study employed mathematical calculation and modelling to get 'exposure metric' as a prediction of emitted power.¹⁷ Another study estimated the magnetic fields produced by power lines for nearby homes by a national grid computer program (EM2D), measuring the distance of the power lines sources

| | Case | es | Contr | ols | Odds Ratio | | | Odds Ratio | |
|-------------------------------------|------------|----------|-------------------------|-------|------------|--------------------|------|--------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% C | 1 | M-H, Fixed, 95% CI | _ |
| Salvan 2015 | 35 | 409 | 37 | 569 | 14.9% | 1.35 [0.83, 2.18] | | | |
| Malagoli 2010 | 2 | 64 | 5 | 256 | 1.0% | 1.62 [0.31, 8.54] | | | |
| Kroll 2010 | 11 | 28968 | 9 | 28968 | 4.7% | 1.22 [0.51, 2.95] | | | |
| Kabuto 2006 | 18 | 312 | 25 | 603 | 8.5% | 1.42 [0.76, 2.64] | | | |
| Schuz 2001 | 9 | 514 | 18 | 1301 | 5.3% | 1.27 [0.57, 2.85] | | | |
| Day 1999 | 39 | 2226 | 44 | 2226 | 22.8% | 0.88 [0.57, 1.37] | | | |
| Green 1999 | 20 | 88 | 23 | 131 | 7.5% | 1.38 [0.71, 2.70] | | | |
| Thomas 1999 | 218 | 232 | 208 | 232 | 6.6% | 1.80 [0.90, 3.57] | | | |
| Dockerty 1998 | 5 | 40 | 1 | 40 | 0.5% | 5.57 [0.62, 50.03] | | | |
| Michaelis 1998 | 9 | 176 | 8 | 414 | 2.4% | 2.74 [1.04, 7.21] | | | |
| Linet 1997 | 58 | 463 | 44 | 463 | 20.3% | 1.36 [0.90, 2.07] | | + | |
| Savitz 1988 | 13 | 115 | 16 | 191 | 5.6% | 1.39 [0.64, 3.02] | | | |
| Total (95% CI) | | 33607 | | 35394 | 100.0% | 1.33 [1.10, 1.60] | | • | |
| Total events | 437 | | 438 | | | | | | |
| Heterogeneity: Chi ² = 8 | 8.06, df = | 11 (P = | 0.71); l ² = | :0% | | | 1 00 | | |
| Test for overall effect: | Z = 3.01 (| P = 0.00 | 3) | | | | 0.02 | Protective Risk | |

Figure 2. Forest plot of the selected studies showing the pooled risk estimates for exposure to non-ionizing radiation against childhood cancer

to the children's house at a specific time.^{18, 20}

Most of the studies carried out questionnaireguided interviews to gather other possible confounders. The questions asked in the interviews were related to parental environmental exposure during prenatal period, childhood exposure, and living environment which might be close to the source of electromagnetic field.^{15, 21-25}

Non-ionizing radiation and childhood cancer

15 articles, only five mentioned the association between non-ionizing radiation and all childhood cancers, as shown in table 2. Leukemia, central nervous system (CNS) tumor, solid tumor, lymphoma and other hematological malignancies are among the common childhood cancers studied. The majority of the studies tried to find the association between non-ionizing radiation (especially EMFs) and childhood leukemia. Generally, all these studies observed weak associations between EMFs and childhood cancer (Table 3). Only two studies showed strong positive associations,^{18, 26} but only one study was significant.

Meta-analysis

12 studies were included in the meta-analysis (Figure 2). For meta-analysis, only studies reporting the exposure to electromagnetic field using the unit μ T were included. Studies using

the unit mG were further included following conversion to μT (1 mG = 0.1 μT). Prior to generating the composite OR, the studies were closely scrutinized and the exposure level of 0.2 μ T (or closest to 0.2 μ T) was extracted onto the standardized summary table. Exposure of less than $0.2 \ \mu T EMF$ was considered as the reference group, whereas exposure of at least 0.2 μ T was considered as the exposed group. Sub-group analysis was performed to ensure that pooled estimate of the risk was done between the most similar groups of studies in relation to methodology and population. All studies, except one,²⁰ showed that exposure to non-ionizing radiation in the form of EMF is a risk for developing childhood cancer. However, only one study showed a statistically significant



Figure 3. Funnel plot of the selected studies for meta-analysis.

| No. | Author (Year) | Design | Country | Type of non- ionizing radiation | Type of cancer ar | Age range of cases id controls (years) | e Magnetio field level | c Method of Assessment | Instrument |
|-------|--|---------------------------------------|--------------------------------|--|---|---|---|--|--|
| 1. | Tabrizi and Bidgoli (2015) | Case-control | Iran | Electromagnetic | ALL | ≤12 | Not mention | ed Not mentioned | Questionnaire |
| 2. | Salvan et al. (2015) | Population- based case- control | Italy | Extremely low frequency magnetic fields (ELF-MF). | Childhood leukemia | <11 | Reference: < 0.2 µT Exposed: | • 48-hr • measurements in the child's | Magnetic field meter (EMDEX II/ |
| Lite) | | | | × / | | | хо 2т | 1 - 1 | × · |
| 3. | Hauri et al. (2014) | Census-based cohort | Switzerland | Radio -frequency electromagnetic fields (RF-EMFs) | Childhood cancer • Leukemia • CNS tum • Other car | <16 a hors hcers | <u>20.2 µ1</u> 0.05V/m 0.05-0.2V/m 0.2V/m | • Estimation | - |
| 4. | Li et al. (2012) base | Population- ed case-control | Taiwan | Radio frequency neoplasms | All paediat | tric ≤15 | All neoplasm (median) • 167.02 WY Leukemia • 168.67 WY Brain neopla • 168.07 WY | ns • Estimation 7s/km ² 7s/km ² 1sm 7s/km ² | - |
| 5. | Malagoli et al. base (2010) | Population- d case-control | Italy | Low frequency electromagnetic radiation | Paediatric hematologi malignanci | <14 ical ies | Reference: <0.1 µT Exposed: >0.1 µT | Estimation | - |
| 6. | Kroll et al. (2010) based | Population- d case-control | United Kingdom | Low frequency electromagnetic radiation | Childhood cancer | <15 | Reference: $<0.2 \ \mu T$ Exposed: $\ge 0.2 \ \mu T$ | • Estimation | - |
| 7. | Kabuto et al. (2006) base | Population- d case-control | Japan | Low frequency electromagnetic radiation | • ALL • AML | ≤15 | Reference: <0.2 µT Exposed: ≥0.2 µT | 1-week-long continuous measurement in the child's bedroom Spot measurements at several points inside and outside of the house. | Magnetic field meter (EMDEX II) Magnetic field meter (EMDEX II) |
| 8. | Schüz et al. (2001) base | Population- d case-control | Germany | Power-frequency magnetic fields | Childhood acute leukemia | ≤15 | Reference: • < $0.2 \ \mu T$ Exposed: $\geq 0.2 \ \mu T$ • i | 24-hr measurements in the child's bedroom 24-hr measurements n the living room • Short-term measurements t several indoor points | Physical Systems FW2a field meter Magnetic field meter (EMDEX II) Magnetic field meter (EMDEX II) |
| 9. | Day et al. P (1999) base | opulation- d case-control | United Kingdom | Power-frequency magnetic fields | Childhood cancer | ≤14 | $\begin{array}{l} \mbox{Reference:} \\ < 0.2 \mu T \\ \mbox{Exposed:} \\ \ge 0.2 \ \mu T \end{array} \ \bullet \end{array}$ | • 48-hr and spot measurements at child's home Spot measurements at school | Magnetic field meter (EMDEX II) Magnetic field meter (EMDEX II) |
| 10. | Green et al. Po (1999) bas contr | opulation- sed case- rol study | Canada | Electric and magnetic field (EMF) | Childhood leukemia | ≤14 | Reference: $<0.2 \ \mu T$ Exposed:` $\ge 0.2 \ \mu T$ i a | Personal monitor worn for 2 days Point-in-time measurement n child's bedroom nd several indoor poi | PositronTM AC Milligauss Meter nts |
| 11. | Thomas et al. P (1999) co b | opulation- ontrol ased case- | United States of America | EMF | Childhood leukemia | ≤9 | $\begin{array}{l} \text{Reference:} \\ <0.125 \ \mu\text{T} \\ \text{Exposed:} \\ \geq 0.125 \ \mu\text{T} \\ \end{array}$ | Spot measurements at indoor and outdo locations 24-hr measuremen n the child's bedroom | at Not or mentioned ts |

| No. | Author (Year) | Design | Country | Type of non- | Type of | Age ra | inge Magnet | ic Method of | f Instrument |
|-----|-----------------|------------|------------|--------------------|------------|---------|--------------------------|--------------------------------------|------------------------------|
| | | | | ionizing radiation | a cancer | of case | es field lev | el Assessmen | t |
| | | | | | a | nd cont | rols | | |
| | | | | | | (years) |) | | |
| 12. | Dockerty et al. | Population | n- New | Low frequency | • Leukemia | ≤14 | $< 0.1 \mu T$ (re | ference) • 24-hr | Positron |
| | (1998) | based case | - Zealand | electromagnetic | • Other | | $0.1 - < 0.2 \mu$ | i measurements | electromagnetic |
| | | control | radiation | field | childhood | | $\geq 0.2 \ \mu T$ | in the child's | dosimeter |
| | | | | | cancers* | | | living room | |
| 13 | Michaelic et al | Population | Germani | Flectromagnetic | Childhood | <15 | Pafaranca | • 24 hr | Magnetic |
| 15. | (1998) | based case | - Ocimany | field (EMF) | leukemia | ~15 | <0.2 µT | measurement | s field meter |
| | (1))0) | control | · | neia (Emi) | louitonnu | | Exposed: | in the child's | (EMDEX II) |
| | | control | | | | | >0.2 µT | bedroom and | 1 |
| | | | | | | | | the living room | m |
| | | | | | | | | Short-term | Magnetic |
| | | | | | | | | measurements | field meter |
| | | | | | | | | at several indoor po | int (EMDEX II) |
| | | | | | | | | Spot measurement | s • Magnetic |
| | | | | | | | | for outdoor | field meter |
| | | | | | | | | | (EMDEX II) |
| 14. | Linet et al. | Population | 1- United | Low frequency | ALL | 2-10 | Reference: | • 24-hr | • Electromagnetic |
| | (1997) | based case | states of | magnetic | | | < 0.2 µT | measurement | field meter |
| | | control | America | field | | | Exposed: $> 0.2 \dots T$ | in the child's | (EMDEX C) |
| | | | | | | | \geq 0.2 μ 1 | | • Electromagnetic |
| | | | | | | | | measurements | field meter |
| | | | | | | | | at several points | (EMDEX C) |
| | | | | | | | | indoor and outdoor | (20022010) |
| 15. | Savitz et al. | Population | - The Unit | ted Magnetic | Any | ≤14 | Reference: | •Instantaneous | Electric Field |
| | (1988) | based case | States of | field | childhood | l | <2.0 mG | measurements | Meter Model |
| | | -control | America | | cancer | | (0.2 µT) | at several | 111/113. |
| | | | | | | | Exposed: | indoor points | |
| | | | | | | | \geq 2.0 mG | | |
| | | | | | | | (0.2 µT) | | |

| Table 2. Characteristics of the select | d studies in the descending o | order of the year of | publication (continued). |
|--|-------------------------------|----------------------|--------------------------|
| | 0 | | |

association.²¹ Pooled risk estimates of the 12 studies, obtained via fixed effects model, showed that children exposed to at least 0.2 µT of EMF non-ionizing radiation ran 1.33 times higher risks of childhood cancer compared to those with less than 0.2 µT exposure (95% CI: 1.10, 1.60). The studies were statistically homogeneous (chisquared P=0.71, I2=0%), and there was also no evidence of publication bias, as evidenced by the funnel plot (Figure 3).

Subgroup analysis was done and studies were grouped according to continent, reference group exposure level, and age group of respondents (Table 4). In the studies conducted in Europe, a more modest association was reported compared to studies done elsewhere, and the pooled estimate was not statistically significant (OR: 1.19, 95% CI: 0.91, 1.56). In terms of reference group exposure level, only three studies reported the findings in a way that the level 0.2 μ T was not possible to be derived into the summary table. In these three studies, although the reference group exposure levels were lower than $0.2 \mu T$, the pooled risk estimate (OR: 1.99, 95% CI: 1.09, 3.63) was actually higher than the overall pooled risk and the highest amongst all subgroups. The pooled risk estimate remained similar with the overall summary OR when the studies were analysed according to age groups of the respondents. For all categories in the three subgroups, studies were homogeneous as evidenced by a non-significant chi-squared test (P>0.10).

Discussion

Association between non-ionizing radiation and childhood cancer

This study showed that there is positive association between non-ionizing radiation and childhood cancer. The odds of childhood cancer in children exposed to at least 0.2 µT of EMFs

| No. | Author (Year) | Type of cancer | Positive cases | Positive controls | OR (95% CI) |
|-----|-------------------------|----------------------------|--------------------------|---------------------|--------------------|
| | | | (Total cases) | (Total controls) | |
| 1. | Salvan et al. (2015) | Childhood leukemia | 35 (409) ^a | 37 (569) | 1.35 (0.83, 2.18) |
| 2. | Li et al. (2012) | All paediatric neoplasms | 1,068(2,046) | 30,666 (60,810) | 1.13(1.01,1.28) |
| | | Leukemia | 368(721) | 10,413 (20,894) | 1.23(0.99,1.52) |
| | | Brain neoplasm | 174(394) | 4,923(11,820) | 1.14(0.83,1.55) |
| 3. | Malagoli et al. (2010) | Paediatric | 2(64) ^b | 5(256) | 1.55 (0.65;367) |
| | | hematological malignancies | | | |
| 4. | Kroll et al. (2010) | Childhood cancer | 11 (28,968) ^c | 9 (28,968) | 0.87 (0.56 - 1.35) |
| 5. | Kabuto et al. (2006) | ALL and AML | 18 (312) | 25 (603) | 1.38* (0.71, 2.70) |
| 6. | Schüz et al. (2001) | Childhood acute leukemia | 9(514) | 18(1301) | 1.55 (0.65;367) |
| 7. | Day et al. (1999) | Childhood cancer | 39 (2226)° | 44 (2226) | 0.87 (0.56 - 1.35) |
| 8. | Green at al. (1999) | Childhood leukemia | 20 (88) | 23 (131) | 1.38* (0.71, 2.70) |
| 9. | Thomas et al. (1999) | Childhood leukemia | 218 (232) | 208 (232) | 2.00 (1.03, 3.89) |
| 10. | Dockerty et al. (1998) | Childhood leukemia | 4 (40) ^d | 5 (40) ^e | 1.4 (0.3, 7.6) |
| | | | 1 (40) | 5 (40) | 15.5 (1.1, 224) |
| 11. | Michaelis et al. (1998) | Childhood leukemia | 9 (176) ^f | 8 (414) | 2.3 (0.8;6.7) |
| 12. | Linet et al. (1997) | ALL | 83 (624) ^g | 70 (615) | 1.24 (0.86, 1.79) |
| | | | 58 (463) ^h | 44 (463) | 1.53 (0.91, 2.56) |
| 13. | Savitz et al. (1988) | Any childhood cancer | 13 (115) | 16 (191) | 1.35 (0.63, 2.90) |

 Table 3. Association between non-ionizing radiation and childhood cancer

*OR was derived indirectly from data in article; a - All leukemias at 95 percentile exposure metric; b- All hematological malignancies at $\geq 2 \mu$ T; c- Leukemias, brain tumours and other cancers at $\geq 0.2 \mu$ T d – Leukemia at 0.1 - < 0.2 μ T; e - Leukemia at $\geq 0.2 \mu$ T; f- Median 24 hours; g- Unmatched analysis; h- Matched analysis.

non-ionizing radiation were 1.33 times higher than those with less than 0.2 μ T exposure (95% CI: 1.10, 1.60). These findings are similar to previous studies^{9,10} where a positive weak association was also reported.

Although meta-analysis via fixed effects model produces an overall risk estimate that shows a positive association between exposure to nonionizing radiation and development of childhood cancer, there are points suggesting that this association is not causal. Firstly, the effect size of the risk estimate is small, less than 1.5 times of the odds, which is even more apparent considering that the meta-analysis had pooled almost 70,000 respondents from 12 studies. Also, there were so many confounders in each individual study that was difficult to ascertain whether the increased risk is truly caused by exposure to nonionizing radiation alone. Furthermore, despite being statistically homogeneous, the studies included for the meta-analysis were not methodologically similar. For instance, it was not possible to derive a reference group for exposure to nonionizing radiation of less than 0.2 µT in three studies. 19,24,29

When subgroup analysis was performed in order to minimize the methodological

discrepancies, it was shown that the risk estimates may not be statistically significant, proving that the association is not likely to be causal. In a recent systematic review with meta-analysis that looked into similar research questions, it was found that the distance between residence and power lines (as a proxy for EMFs exposure; hence, non-ionizing radiation exposure) played an unclear role in developing the risk of childhood leukaemia.¹⁰ In addition, most studies conducted in this area are case-control studies; hence, the difficulty associated with elucidating a true temporal relationship whereby exposure to nonionizing radiation precedes the pathogenesis of childhood cancer.

There are also data pointing to the causal association between non-ionizing radiation and childhood cancer. Although not proven, nonionizing radiation has be postulated to have a biological plausibility to be carcinogenic. Nonionizing radiation possesses sufficient energy for the excitation of an electron to a higher energy state, causing non-mutagenic effects in biological tissues and plausible carcinogenic changes in the long-term. There are also studies and reviews which have found significant associations between non-ionizing radiation and childhood

| Table 4. Summary statistics of s | sub-group analysis for the | e association betwee | en exposure to non- | ionizing radiation and childhood cancer | | | | |
|---|----------------------------|------------------------------|---------------------|---|--|--|--|--|
| Subgroups N | umber of Studies | <i>P</i> -value ^a | I2 (%) ^b | Fixed Effects OR (95% CI) | | | | |
| All studies | 12 | 0.71 | 0 | 1.33 (1.10, 1.60) | | | | |
| By continent | | | | | | | | |
| Europe | 6 | 0.41 | 1 | 1.19 (0.91, 1.56) | | | | |
| North America | 4 | 0.92 | 0 | 1.44 (1.08, 1.93) | | | | |
| Asia and Oceania | 2 | 0.24 | 29 | 1.63 (0.91, 2.92) | | | | |
| By reference exposure | | | | | | | | |
| Reference group $< 0.2 \ \mu T$ | 9 | 0.71 | 0 | 1.27 (1.05, 1.55) | | | | |
| Reference group other than a | above 3 | 0.61 | 0 | 1.99 (1.09, 3.63) | | | | |
| By age range | | | | | | | | |
| 0-14 years old | 9 | 0.52 | 0 | 1.26 (0.99, 1.62) | | | | |
| 0-9 or 10 years old | 3 | 0.76 | 0 | 1.43 (1.07, 1.90) | | | | |
| a: P-value for heterogeneity (chi-squared); b I2 statistics for heterogeneity quantification. | | | | | | | | |

cancer.^{9,11,12,31} Although the effect sizes for risk estimates are not more than 2, a number of studies have consistently replicated the result that an increased risk of childhood cancer with exposure to non-ionizing radiation.

Strengths and limitations

The present is the latest review to include studies related to all childhood cancers. Prior reviews have only focused on childhood blood malignancy or leukaemia. In this review, the reference group for exposure to non-ionizing radiation was further standardized as much as possible in order to ensure methodological robustness. As far as weaknesses are concerned, all studies included in meta-analyses were casecontrol studies, which reduces the strength of the obtained results because case-control studies are subjected to recall, interviewer, and selection bias and other methodological problems associated with such design. Moreover, each study had its own definition of the age limit for the study population. Those aged more than the age limit were not considered or categorized as childhood cancer; thus, not included as cases or controls. Furthermore, most childhood cancer cases were taken from cancer registry; thus, the duration of exposure to non-ionizing radiation prior to diagnosis could not be ascertained. Apart from that, the children were considered as exposed to non-ionizing radiation based on current residential area and proximity to the source of EMFs. Pooling all childhood cancers together may also dilute the importance and contribution of non-ionizing

radiation to the development of particular cancers. We were also unable to find a significant association between non-ionizing radiation and childhood cancer based on age categorization in those studies. Nevertheless, we hold that this approach is the most optimal due to the lack of similar precedent reviews.

Conclusions

Based on the current meta-analysis, it cannot be concluded that children exposed to non-ionizing radiation run higher risks of contracting childhood cancer compared to those who are not exposed, as claimed by the previous reviews. Although only a weak association can be ascertained to date, non-ionizing radiation is still a public health issue. Therefore, concerns about non-ionizing radiation and childhood cancer ought not to be neglected.

Conflict of Interest

None declared.

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